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13. ABSTRACT (Maximum 200 Words) This study proposed to evaluate contrast-enhanced ultrasound imaging with a microbubble contrast agent in 300 subjects over a period of 3 years in order to improve the detection of prostate cancer. Although the grant period began 8/1/2001, patient recruitment actually commenced on 10/1/2001. Between 10/15/2001 and 7/31/2002 a total of 103 subjects provided informed consent. Laboratory blood tests (PSA) and ultrasound evaluations were completed on all 103 subjects (including the ultrasound interpretation worksheet of the primary reviewer). An independent blinded reader has completed review of the first 47 subjects. Pathological review for the presence and grade of cancer has been completed for all 103 subjects. CD31 staining for microvessel density is in progress. Microvessel density counting will begin in August 2002. All available data has been entered into a computer database using an Excel spreadsheet. A preliminary analysis of the data from the first 56 subjects was incorporated into an abstract that has been accepted for presentation at the 60 th annual meeting of the Mid-Atlantic section of the American Urological Association (see appendix). Based upon the current rate of recruitment (10 patients/month), study recruitment will require an additional 20 months. If the end date for the study is extended to 9/31/04, the study protocol is progressing on target.				
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INTRODUCTION:

The objective of this study is to utilize ultrasound imaging with intravenous infusion of a microbubble contrast agent to improve the detection of prostate cancer, and to identify those cancers which are clinically significant. Over a three year period, three hundred subjects with suspected cancer of the prostate are to be enrolled. These patients will be imaged with conventional and intermittent ultrasound both before and after administration of the contrast agent. Based upon a comparison of ultrasound findings with biopsy results, this study will attempt to demonstrate that intermittent ultrasound imaging with a contrast agent results in improved detection of prostate cancer. Furthermore, ultrasound findings with the contrast agent are to be correlated with Gleason score and PSA in order to determine whether intermittent imaging can selectively identify clinically significant cancers.

BODY:

Statement of Work tasks:

#1 - Ultrasound contrast studies: One hundred and three subjects have been recruited into the study to date. Each subject has provided written informed consent and was evaluated with the required laboratory studies (PSA) prior to participation in the ultrasound contrast protocol. The examining physician (Dr. Ethan Halpern) has completed an ultrasound image interpretation worksheet for each of these subjects. Because of paperwork delays, patient recruitment began in October 2001, two month after the start date of the grant. Assuming that the end date of the study is extended by two months to 9/31/2004, this portion of the study is progressing on target.

#2 – Pathologic evaluation: Specimens from all 103 subjects have been evaluated by standard pathologic evaluation. A pathology interpretation worksheet has been completed by our pathology consultant (Dr. Peter McCue). Approximately one-third of the subjects were found to have cancer. Additional tissue sections from each biopsy block have been cut for CD31 staining. Technical problems were encountered with the microvessel density counting system. These have now been fixed, and microvessel density counting of specimens will commence in August 2002.

#3 – Database entry: A database has been established, and all ultrasound and pathology data available to date have been entered by the research coordinator.

#4 – Interim statistical evaluation: planned for month 13 will be performed in October 2002 (because of the two month delay in starting patient recruitment).

#5 – Consensus interpretations: blinded reviews of the ultrasound studies are performed by a second reader (Dr. Stephen Strup). Blinded reads have been completed for the first 47 cases.

#6 – Publications: a preliminary abstract for the first 56 subjects was accepted for presentation at the annual meeting of the mid-Atlantic section of the American Urological Association.

KEY RESEARCH ACCOMPLISHMENTS:

- Successful infusion of ultrasound contrast in 103 subjects
- Visible vascular enhancement within the prostate of all subjects studied to date
- Detection of three-fourths of cancer foci based upon contrast enhancement to date

REPORTABLE OUTCOMES: one abstract accepted for presentation (see attached – page 6).

CONCLUSIONS:

Intravenous infusion of a microbubble contrast agent provides sonographically visible enhancement of the prostate. This enhancement can be used to guide biopsy of the prostate into areas of increased vascular flow. In our study, targeted biopsies of areas with increased blood flow detected approximately three-fourths of cancers found in our population. In the initial 56 subjects, several cancers were not identified at the apex of the gland based upon contrast-enhanced flow patterns (see abstract). Follow-up is required to determine whether this technique detects all “significant cancers”, or whether the contrast technique misses important cancers.

Comparison of an unrestricted targeted approach to a sextant approach
for contrast-enhanced Biopsy of a Prostate

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Purpose: Sextant biopsy of the prostate systematically samples the base, mid-gland and apex. Recent studies have demonstrated improved detection of prostate cancer based upon targeted biopsy with microbubble contrast agents. Our study evaluated cancer detection with two different contrast-enhanced biopsy strategies: an unrestricted targeted approach that focused on the most suspicious areas in the outer gland, and a modified sextant approach that targeted the most suspicious area within each sextant.

Methods: Fifty six subjects with an elevated PSA ($> 4\text{ng/ml}$) or abnormal digital rectal examination were evaluated by transrectal sonography during infusion of a microbubble contrast agent (Imavist – Alliance Pharmaceuticals). Sonography was performed with the Sonoline Elegra (Siemens Medical Systems) using a 6.5MHz end-fire transducer. Up to four unrestricted targeted biopsy cores were directed toward the most suspicious areas of the outer gland during contrast-enhanced harmonic gray scale and Doppler imaging. Six additional biopsy cores were obtained in a modified sextant distribution to target the most suspicious area in each sextant. Each sextant with no suspicious area was sampled with a laterally directed core.

Results: Cancer was detected in 77 biopsy cores from 19 of 56 subjects (34%). Cancer was found in 18% (34/193) of unrestricted targeted cores and in 13% (43/336) of targeted sextant cores. Of 19 subjects with cancer, 15 were detected by both techniques. Three subjects were detected only by targeted sextant biopsy while 1 subject was detected only by unrestricted targeted biopsy. The 3 subjects missed by unrestricted targeted biopsy included two Gleason 6 cancers (at right apex and left apex) and one Gleason 8 cancer (at right apex). While 42% (18/43) of positive targeted sextant cores were obtained at the gland apex, only 18% (6/34) of positive unrestricted targeted cores were obtained from the gland apex. Only 12% (23/193) of unrestricted targeted biopsies were directed to the apex.

Conclusion: Although the “per-core” cancer detection rate of unrestricted targeted biopsy was slightly higher when compared to the targeted sextant approach, the unrestricted technique missed cancers at the apex of the prostate. The low proportion of biopsy cores targeted to the apex suggests that contrast enhancement is less conspicuous at the apex. In order to maximize cancer detection, we recommend that any targeted biopsy strategy should include cores at the apex of the prostate.